CLINICAL EVIDENCE

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Non-metastatic prostate cancer

Questions: What are the effects of treatment in men with clinically localized prostate cancer? In men who have received primary treatment and remain asymptomatic, should androgen deprivation be offered when raised concentrations of prostate specific antigen are detected? What are the effects of treatment in men with locally advanced prostate cancer?

INTERVENTIONS

Clinically localized prostate cancer

Unknown effectiveness
Watchful waiting
Radical prostatectomy
External beam radiation therapy
Brachytherapy
Cryosurgery
Androgen deprivation
Androgen deprivation in asymptomatic men with raised concentrations of prostate-specific antigen after early treatment

Locally advanced prostate cancer

Beneficial
Radiation plus androgen deprivation (improves survival compared with radiation therapy alone)

Likely to be beneficial
Androgen deprivation initiated at diagnosis

Unknown effectiveness
Radiation therapy alone

DEFINITION

Prostatic cancer can be staged according to two systems: the tumor, node, metastasis (TNM) classification system and the American urologic staging system (see box). Non-metastatic prostate cancer can be divided into clinically localized disease and advanced disease.

Summary points

In men with clinically localized disease

- The data we found do not provide clear evidence for the superiority of any one treatment, including androgen deprivation. Limited data from one randomized control trial (RCT) suggest, however, that radical prostatectomy may reduce recurrence compared with radiation treatment.
- We found limited data from RCTs suggesting that radical prostatectomy or external beam radiation therapy may not improve survival or reduce the risk of metastatic disease or the need for palliative treatment compared with watchful waiting.
- External beam radiation therapy, brachytherapy, and cryosurgery have not been compared with watchful waiting in RCTs.
- We found no RCTs addressing the question of whether androgen deprivation should be offered to asymptomatic men in whom raised concentrations of prostate-specific antigen are detected after primary treatment or during watchful waiting.

In men with locally advanced disease

- We found limited evidence from RCTs suggesting that androgen deprivation initiated at diagnosis improves survival and reduces the risk of major complications compared with treatment deferred until disease progression.
- A systematic review found that adding androgen deprivation to radiation treatment improves survival compared with treatment with radiation alone.
- We found no good evidence that radiation alone is beneficial for survival.

INCIDENCE AND PREVALENCE

Prostate cancer is the most common nondermatologic malignancy worldwide and the second leading cause of deaths from cancer in men in the United States.[1] It caused an estimated 184,500 new cases and 39,200 deaths in 1998.[2] For a 50-year-old man with a life expectancy of 25 years, the lifetime risk of microscopic prostate cancer is about 42%, the risk of clinically evident prostate cancer is 10%, and the risk of fatal prostate cancer is 3%.[3]

Timothy J. Wilt
Northwest Prostate Institute
1560 North 115th Street, Suite 209
Seattle, WA 98133

Michael K. Brawer
Center for Chronic Diseases Outcomes Research
Minneapolis VA Hospital 111-0
One Veterans Drive
Minneapolis, MN 55417

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Prostatic cancer staging systems

Tumor, node, metastasis (TNM) classification system

Tumor

To	Clinically unsuspected
T1	Clinically inapparent (not palpable or visible by imaging)
T2	Tumor confined within prostate
T3	Tumor outside capsule or extension into vesicle
T4	Tumor fixed to other tissue

Nodes

No	No evidence of involvement of regional nodes
N1	Involvement of regional node

Metastases

Mo	No evidence of distant metastases
M1	Evidence of distant metastases

American urologic staging system

Stage A	No palpable tumor
Stage B	Tumor confined to the prostate gland
Stage C	Extracapsular extension
Stage D	Metastatic prostate cancer
Stage D1	Pelvic lymph node metastases
Stage D2	Distant metastases

ETIOLOGY

Risk factors include age, family history of prostate cancer, black race, and, possibly, higher dietary fat intake.

PROGNOSIS

The chance that men with well to moderately differentiated, palpable, clinically localized prostate cancer will remain free of symptomatic progression is 70% at 5 years and 40% at 10 years.[4] The risk of symptomatic disease progression is higher in men with poorly differentiated prostate cancer.[5] Morbidity from local or regional disease progression includes hematuria, bladder obstruction, and lower extremity edema. Despite widespread testing for prostate-specific antigen and increased rates of radical prostatectomy and radiation therapy, population-based studies show that rates of death from prostate cancer in the United States have declined by only about 1/100,000 men since 1992.[6,7] Regions of the United States that have experienced the greatest decreases in mortality are those with the lowest rates of testing for prostate-specific antigen and treatment with radical prostatectomy or radiation.[7] Countries with low rates of testing and treatment do not consistently have higher age-adjusted rates of death from prostate cancer than countries with high rates of testing and treatment, such as the United States.

AIMS

To prevent premature death and disability while minimizing the adverse effects of treatment

OUTCOMES

Survival; time to progression; response in terms of symptoms and signs; quality of life; adverse effects of treatment

METHODS

We searched for systematic reviews and RCTs using the search strategy of the Department of Veterans Affairs Cochrane Review Group on Prostatic Diseases (Cochrane Library and MEDLINE to the end of 1998). We reviewed all systematic reviews and RCTs that were identified.

Question: What are the effects of treatment in men with clinically localized prostate cancer?

OPTION: WATCHFUL WAITING

We found no direct evidence from RCTs that watchful waiting improves the length or quality of life in men with clinically localized prostate cancer compared with other management strategies.

Benefits

We found two systematic reviews.[1,8] In men managed by watchful waiting, prospective cohort studies report 15-year disease-free survival of 80%, ranging from 95% for well-differentiated cancers to 30% for poorly differentiated cancers.[9,10]

Versus early androgen deprivation, we found no RCTs.

Versus radical prostatectomy, we found 1 RCT (see below).[11]

Harms

Expectant management does not remove a cancer that may progress and cause death or disability.

Comment

There is about a 10-year lead time between the detection of cancers by raised concentrations of prostate-specific antigen and detection by digital rectal examination or the development of symptoms. This means that outcomes are likely to be similar in men with palpable tumors who are followed for 15 years and men whose tumors are detected in raised concentrations of prostate-specific antigen who are followed for 25 years.

OPTION: RADICAL PROSTATECTOMY

Limited data from RCTs provide no evidence that radical prostatectomy improves outcome compared with watchful waiting. It may reduce the risk of metastases compared with external beam radiation therapy. Radical prostatectomy carries the risks of major surgery and of sexual and urinary dysfunction.

Benefits

We found two systematic reviews.[1,8]

One RCT compared radical prostatectomy versus watchful waiting in 142 men with clinically localized prostate cancer. After a median follow-up of 23 years (range, 19-27 years), no difference in survival was detected between the two groups (median survival 10.6 years with prostatectomy versus 8 years with watchful waiting, no confidence interval quoted).[11]

One RCT compared radical prostatectomy versus external beam radiation in 97 evaluable men with clinically localized prostate cancer. Men receiving radiation treatment had an increased risk of metastases (4 "treatment failures" with prostatectomy versus 17 with radiation treatment).[12]

Harms

Fatal complications have been reported in 0.5% to 1% of men treated with radical prostatectomy and may exceed 2% in men aged 75 years and older.[13] Nearly 8% of men older than 65 years had major cardiopulmonary complications within 30 days of an operation. The incidence of other adverse effects of surgery was over 80% for sexual dysfunction, 30% for urinary incontinence requiring pads or clamps to control wetness, 18% for urethral stricture, 3% for total urinary incontinence, 5% for fecal incontinence, and 1% for bowel injury requiring surgical repair.[1,14-16]

Comment

Both RCTs of radical prostatectomy were conducted before the advent of tests for prostate-specific antigen and were too small to exclude a clinically important difference between groups. Radical prostatectomy may benefit selected groups of men with localized prostate cancer, particularly younger men with higher-grade tumors. The available data suggest, however, that in most men the potential benefits in quality-adjusted life expectancy are small at best and sensitive to patients' preferences.[8] Studies have found no differences among groups treated with radical prostatectomy, radiation, or watchful waiting when evaluating general health-related quality of life.[17] Two ongoing trials are comparing radical prostatectomy versus watchful waiting.[18,19]

OPTION: EXTERNAL BEAM RADIATION THERAPY

We found limited evidence from one small RCT that, compared with radical prostatectomy, external beam radiation therapy increases the risk of metastases in men with clinically localized prostate cancer. It has not been compared directly to watchful waiting.

Benefits

Versus watchful waiting, we found no RCTs.

Versus radical prostatectomy, we found one RCT.[12]

Harms

The RCT made no mention of adverse effects of treatment.[12] A survey of men treated with external beam radiation therapy reported that 7% wore pads to control wetness, between 23% and 32% of men were impotent, and 10% reported problems with bowel dysfunction.[20] Treatment-related mortality is <0.5%.[1] External beam radiation therapy requires that men return for daily outpatient treatment for up to 6 weeks.

Comment

Up to 30% of men with clinically localized prostate cancer treated with radiotherapy still have positive biopsies 2 to 3 years after treatment.[21] Up to 60% have biochemical evidence of recurrence, which may reflect either distant or local recurrence.[22,23]

OPTION: BRACHYTHERAPY

We found no direct evidence from RCTs that brachytherapy improves the length or quality of life in men with clinically localized prostate cancer.

Benefits

We found no systematic reviews or RCTs.

Harms

Complication rates reported from case series include urinary retention (6%-7%), incontinence (1%-6%), cystitis/urethritis (4%-7%), proctitis (1%-12%), and impotence (6%-50%).[24] Long-term outcomes from a representative national sampling of men have not been reported.

OPTION: CRYOSURGERY

We found no direct evidence from RCTs that cryosurgery improves the length or quality of life in men with clinically localized prostate cancer.

Benefits

We found no systematic reviews or RCTs.

OPTION: ANDROGEN DEPRIVATION

We found no direct evidence from RCTs that androgen deprivation improves the length or quality of life in men with clinically localized prostate cancer.

Benefits

We found no systematic review or RCTs.

Harms

Adverse effects of androgen deprivation include osteoporosis, weight gain, hot flushes (10%-60%), loss of muscle mass, gynecomastia (5%-10%), impotence (10%-30%), and loss of libido (5%-30%).[25] These adverse effects are particularly

important when considering treatment in men with a long life expectancy or treatment duration, such as younger men with lower-grade cancers.

Comment

Treatment with androgen deprivation may help to relieve anxiety in men diagnosed with clinically localized prostate cancer by giving the sense that something is being done.

Question: In men who have received primary treatment and remain asymptomatic, should androgen deprivation be offered when raised concentrations of prostate-specific antigen are detected?

The effects of initiating androgen suppression when prostate-specific antigen rises or persists after primary treatment have not yet been evaluated in RCTs.

Benefits

We found no systematic reviews or RCTs.

Harms

Potential harms include unnecessary or inappropriate treatment.

Comment

Clinicians often monitor blood concentrations of prostate-specific antigen and offer androgen suppression when these rise. Consequently, more men with disease persistence are being considered for androgen suppression, and treatment is being initiated earlier in the natural course of the disease. RCTs are needed to evaluate the effectiveness of this approach and of intermittent treatment during which androgen suppression is initiated when concentrations of prostate-specific antigen rise after primary treatment and is discontinued when the antigen concentrations return to baseline.

Question: What are the effects of treatment in men with locally advanced prostate cancer?

OPTION: ANDROGEN DEPRIVATION

RCTs have found that in men with locally advanced disease androgen deprivation initiated at diagnosis reduces complications and may improve survival. Androgen deprivation improves survival in men with locally advanced disease treated with radiation.

Benefits

Versus no initial treatment, we found one systematic review that identified no recent RCTs. Three RCTs performed between 1960 and 1975 compared androgen deprivation (diethylstilbestrol, orchiectomy, or estrogens) versus no initial treatment in about 4000 men with all stages of prostate cancer. They found no difference in overall survival. Reanalysis of updated data from these RCTs provided tentative evidence of a modest survival advantage with androgen deprivation.[26]

Comparing immediate (initiated at diagnosis) versus deferred androgen deprivation, we found one systematic review that identified three RCTs (n=2143), two of which were conducted in the 1960s.[25] None had a uniform protocol for initiating deferred treatment, so deferred treatment in these trials reflects the varied practices of the treating clinicians. Meta-analysis found no significant survival difference at 5 years between immediate androgen deprivation compared with deferred androgen deprivation (hazard ratio 0.914, 95% confidence interval [CI] 0.81-1.03).[25] The more recent trial, which included 938 men with stage C (locally advanced) and D (asymptomatic metastatic) disease, reported a survival benefit from immediate treatment (62% of deaths were from prostate cancer compared with 71% in the deferred treatment arm, P<0.001). The survival benefit was limited to men with stage C disease.[27] Immediate androgen deprivation almost halved the risk of major complications, such as pathological fractures (absolute risk 2.3% vs 4.5% with deferred treatment), spinal cord compression (absolute risk 1.9% vs 4.9%), ureteric obstruction (absolute risk 7% vs 11.8%), and extraskeletal metastases (absolute risk 7.9% vs 11.8%). The report did not quote confidence intervals nor make clear the time interval over which outcomes were recorded, though this seemed to be at least 10 years. Again, the lower incidence of complications was more apparent in men presenting with stage C disease.

Radiation therapy plus androgen deprivation

We found one systematic review, which identified four RCTs comparing early versus deferred androgen deprivation in men receiving external beam radiation therapy. Early androgen deprivation was initiated at the same time as radiation treatment for locally advanced or asymptomatic clinically evident metastatic prostate cancer and continued until the development of hormone-refractory disease. The deferred group received radiation treatment alone, with androgen deprivation initiated only in those in whom the disease progressed.[25] Meta-analysis found a difference in overall 5-year survival in favor of early androgen deprivation compared with deferred deprivation (hazard ratio 0.63, 95% CI 0.48-0.83; percent surviving at 5 years 76.5% vs 68.2%, absolute risk reduction 8.3%; number needed to treat at 5 years = 12).[25]

Harms

Adverse events were not well reported in the RCTs. Earlier initiation of androgen deprivation means longer exposure to adverse effects, which include osteoporosis, weight gain, hot flushes (10%-60%), loss of muscle mass, gynecomastia (5%-10%), impotence (10%-30%), and

loss of libido (5%-30%).[25] These adverse effects are particularly important when considering treatment of men with a long life expectancy or younger men with lower-grade cancers.

Comment

The RCTs conducted in the 1960s[25] included men who were older and had more advanced cancers than those in the more recent RCT.[27] RCTs are needed to evaluate the effectiveness of neo-adjuvant androgen deprivation to downstage the tumor before surgery when disease extends beyond the capsule.

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PRACTICE POINT

Fancy drugs for worried folks

When Mrs. Boronowski, aged 67, went to Dr. Jingle for her nervous indigestion and multiple allergies, she left his office with a whole bunch of prescriptions. She was given omeprazole ($4 a tablet), even though belladonna or a bottle of amphojel would have done as well. To calm her shattered nerves she received buspirone ($1.30 a tablet), because diazepam is now too common to be effective. For her allergies, Dr. Jingle prescribed loratidine ($2.20 a tablet), because chlorpheniramine at 2¢ would have made her too sleepy to tolerate her tranquilizer; and he also gave her the newest hypnotic, zolpidem ($1.70 a tablet), highly recommended by the friendly detail man. She also takes atorvostatin ($3.60 a tablet), because dieting is so difficult; a multivitamin B tablet (for energy), yeast, ascorbic acid, vitamin E, and for her systolic hypertension, losartan ($1.30 a tablet)—why prescribe mere generic atenolol?

When Mrs. Boronowski returned home, she looked at the pharmacist's bill. She sent it to her insurance company and immediately felt better.

In the future, if President Clinton has his way, she will send her bill to Medicare, for being over 65, she would be entitled to such coverage. At present one third of Medicare recipients are reported to have no drug coverage. Mr. Clinton would like to remedy this by providing full coverage for everybody, including Mrs. Boronowski. This will probably become an election issue and a political football. The pharmacy industry fears that price controls will surely follow and argues that they will kill the golden research goose that has revolutionized modern therapeutics. Mrs. Boronowski's bill may indeed drop by 20%, but Dr. Jingle will continue to prescribe the newest and dearest drugs, and the taxpayer will foot the bill.

Meanwhile, down at the gas station, Mr. Suggs, who pumps gas for small wages, has a painful duodenal ulcer relieved only by omeprazole ($4 a tablet), which he has to pay for himself because he has no insurance. His neighbor has had a kidney transplant and cannot afford to buy his antirejection drugs. But another neighbor has a "nervous condition," a limp, takes cocaine, gets a bagful of free medicine from Medicaid each month, and watches soap operas most of the day.

I do not know if there ever was an ancient goddess of reason. But if there were, she assuredly remains perched high on Mount Olympus and has not yet descended among the mortals.

George Dunea, Cook County Hospital, Chicago, IL